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Reactivity of the Triple Ion and Separated Ion Pair of Tris(trimethylsilyl)methylithium with Aldehydes: A RINMR Study

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The high steric hindrance of tris(trimethylsilyl)methylithium (**1**) results in unique structural features that allow mechanistic probes not possible with normal lithium reagents. In THF solution below $-100\text{ }^{\circ}\text{C}$, **1** exists as three species in slow exchange on the NMR time scale, the monomeric contact ion pair **1C**, the solvent-separated ion pair **1S**, and the dimeric triple ion **1T** (Scheme 1).^{1a,2} The unprecedented high barriers to interconversion allowed us to test their individual reactivity under non-Curtin–Hammett conditions using low-temperature rapid-injection NMR (RINMR).^{1b}

Injection of methyl iodide into solutions of **1** (Figure 1) showed no reaction of **1T** at $-132\text{ }^{\circ}\text{C}$, but disappearance of the signals for **1S** in less than the time scale of injection and mixing (1 s, $k_{1S-\text{MeI}} > 2\text{ s}^{-1}$),^{1b} and a measurable rate for **1C** ($k_{1C-\text{MeI}} = 0.04\text{ s}^{-1}$). A similar experiment at $-86\text{ }^{\circ}\text{C}$ resulted in immediate ($<1\text{ s}$) disappearance of **1C** and **1S** and the decay of **1T** over a period of several hours ($k_{1T-\text{MeI}} = 3 \cdot 10^{-5}\text{ s}^{-1}$). **1T** and **1C** reacted at rates independent of electrophile concentration,³ thus both must first dissociate to **1S**.

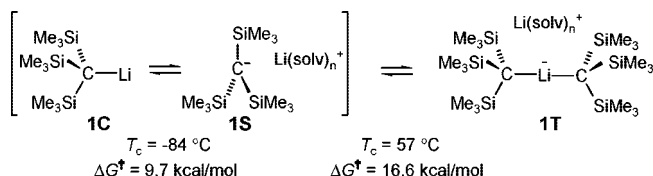
From these data, we can calculate that **1S** is ≥ 50 times as reactive as **1C** toward MeI. An upper limit on the rate MeI reacts with **1T** at $-132\text{ }^{\circ}\text{C}$ of $k_{1T-\text{MeI}} \leq 4 \times 10^{-10}\text{ s}^{-1}$ can be calculated from the temperature dependence of the reaction. Thus, **1S** is at least 5×10^{10} times as reactive as **1T**. These relative rates are likely large underestimates since the reaction of **1S** is faster and the reactions of **1T** and **1C** are slower than the measured rates.

The reaction with aldehydes is more complex.⁴ The reactivity profile of **2** and **3** with **1S** and **1C** was nearly identical to that of MeI. Conversely, the reaction of **1C** in the presence of **4b** is slowed by a factor of 100 compared to the “normal” dissociation of **1C** to **1S**. This unexpected effect was not studied.

However, all three aldehydes did appear to react with **1T**. Direct rate measurements showed that **1T** displayed a reaction order of 0.8 in **2** due to competitive dissociation to **1S** and **1C**. Interestingly, the electron-rich **4** reacts faster than the deficient **2** ($k_{\text{rel}}[\text{direct}]$ in Figure 2). Activation parameters for reaction of **1T** with **2**, **3**, and **4b** were determined from the temperature dependences of the rates. Extrapolation to $-131\text{ }^{\circ}\text{C}$ gave estimates of $k_{1S}/k_{1T} \geq 220\,000$ for **4b**, $\geq 3.7 \times 10^7$ for **3**, and $\geq 1.4 \times 10^9$ for **2**.

To confirm the inverse of the normally expected Hammett relationship for the reaction of aldehydes with **1T**, we performed competition experiments. Solutions containing only **1T** were prepared by first scavenging **1C** and **1S** by addition of MeI (at $-78\text{ }^{\circ}\text{C}$ (**1T** does not react with MeI on this time scale), followed by the addition of a binary mixture of aldehydes. Relative rates were calculated from product ratios and were found to be in the normal order expected for nucleophilic addition to aldehydes ($k_{\text{rel}}[\text{competition}]$ in Figure 2).

Scheme 1. Tris(trimethylsilyl)methylithium DNMR dynamics in 3:2 THF/Et₂O^{1a}



Since competition experiments are routinely used to measure relative rates, and from them absolute rates, this reversal merited some attention. We were aided in this endeavor by observations on the effect of the strong coordinating solvent HMPA.^{1c} Under equilibrium conditions, addition of excess HMPA converts **1** completely to the separated ion pair **1S** (with $\text{Li}(\text{HMPA})_4^+$ as counterion).^{1a} HMPA solvation resulted in a notable reduction in reactivity toward aldehydes. The reaction of **1S**–HMPA with **2** at $-131\text{ }^{\circ}\text{C}$ was still too fast to measure ($k > 2\text{ s}^{-1}$), but that with **3** was observable ($k = 0.012\text{ s}^{-1}$). Extrapolation of the observed rates for **4b** from measurements at $T > -84\text{ }^{\circ}\text{C}$ gave a $k_{1S-\text{HMPA}-4b} = 2.3 \times 10^{-10}\text{ s}^{-1}$ at $-131\text{ }^{\circ}\text{C}$. The aldehydes have the expected

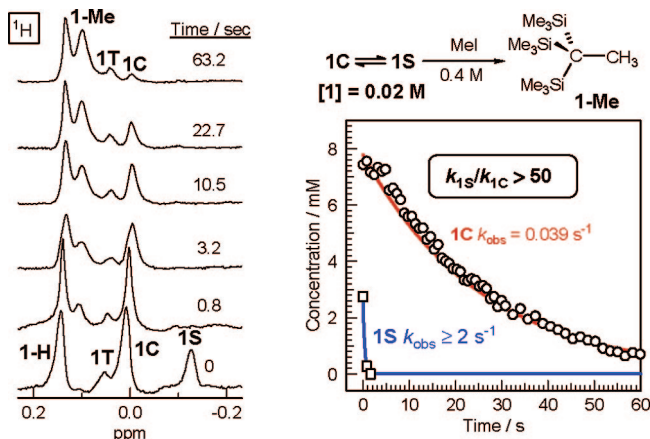


Figure 1. Selected ¹H NMR spectra (trimethylsilyl signals) and rate plot of a RINMR experiment of MeI (0.10 mL neat) injected into a solution of **1** (0.02 M) in 1:3 THF/Me₂O at ca. $-132\text{ }^{\circ}\text{C}$.

	2	3	4
$k_{\text{rel}}[\text{direct}]$	1	20	200 (4a), 510 (4b)
$k_{\text{rel}}[\text{competition}]$	1	0.3	0.03 (4a)

Figure 2. Relative rates of reaction of **1T** with aldehydes **2–4** at $-78\text{ }^{\circ}\text{C}$, measured directly by RINMR or by competition experiments

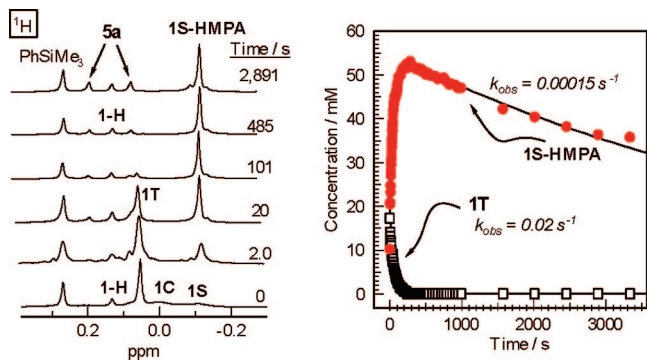
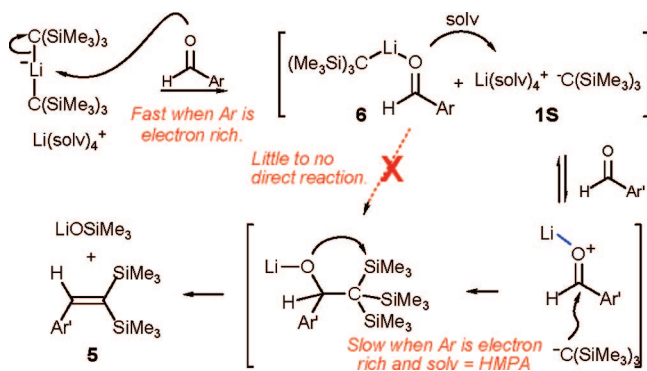


Figure 3. Injection of an ethereal solution of **4a** (1 equiv) and HMPA (5 equiv) into **1** (0.06 M) in 1:3 THF/Me₂O at -80°C .

Scheme 2. Proposed Mechanism



order of reactivity toward **1S**–HMPA based on their electrophilicities: **2** > **3** \gg **4b**. HMPA retarded the reaction of **4b** with **1S** by a factor of at least 10^{10} . This is the first direct measurement of the Lewis acid activating effect of a THF-solvated lithium cation in an organometallic addition to an aldehyde.⁵

If HMPA was injected into a solution of **1** below -70°C , **1C** was rapidly converted to **1S**–HMPA. **1T** was also converted to **1S**–HMPA but at the same rate as the known dissociation rate of **1T** to **1S/1C** in the absence of HMPA. Thus, HMPA does not assist in the dissociation of **1T** by coordination to the central lithium⁶ nor does the dissociation involve electrophilic attack on the triple ion by Li⁺. This observation, and the fact that **1S**–HMPA reacts only very slowly with **4**, allowed a key experiment that helped identify the source of the reactivity reversal depicted in Figure 2. If HMPA was first injected into **1** at -94°C , leading to a solution containing only **1S**–HMPA and **1T**, followed by an injection of **4a**, then **1T** was smoothly converted to **1S** without significant formation of the Peterson product **5a**. The same results were obtained when HMPA and **4a** or **4b** were injected simultaneously (Figure 3), or when a catalytic amount of the aldehyde was used. The rate is identical to the rate of reaction of **4** with **1T** in the absence of HMPA.⁷ Thus **4** catalyzes the dissociation of **1T**, but the monomers formed are inactivated by HMPA. In the absence of HMPA, **1S** reacts rapidly with **4**.

We can thus make the proposal shown in Scheme 2. In the individual kinetic runs, the rate-determining step is aldehyde-catalyzed dissociation of **1T** to the monomers.⁶ The more basic **4** is a better catalyst than **2** and displays the faster rate by RINMR kinetic measurements ($k_4 > k_2$).⁸ The likely first formed intermediate **6**, which would normally be considered competent to form product,⁹ does not do so but dissociates to **1S**, which then adds to the aldehyde. In competition experiments, the more basic **4** causes

dissociation of **1T**, but the formed monomers react preferentially with the more electrophilic **2**, giving $k_2 > k_4$. The high effectiveness of **4** as a catalyst for dissociation of **1T** can be ascribed to the small size of the nucleophilic oxygen in **4** compared to that in HMPA^{10a} (which is an ineffective catalyst).

Using RINMR, competition experiments, and the remarkable rate-retarding effect of the cosolvent HMPA,¹¹ we have observed differing rate- and product-determining steps that lead to contradictory rate effects in an organolithium–aldehyde reaction. Given the enormously greater reactivity of lower over higher aggregates seen for several lithium reagents and the resultant tendency to dissociate to lower aggregates prior to reaction,^{1b,10b,12} the phenomenon described here is plausible for other reactions with Lewis basic substrates that can actively participate in the deaggregation process. This study also illustrates the critical role of lithium catalysis on carbonyl reactivity.

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Supporting Information Available: Additional experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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